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Cutaneous Lymphomas: An Update. Part 2: B-Cell Lymphomas and Related Conditions

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Abstract: Primary cutaneous B-cell lymphomas (PCBCL) are the second most common form of primary cutaneous lymphomas and account for approximately 25%–30% of all primary cutaneous lymphomas. Both forms of low-grade malignant PCBCL, primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous marginal zone lymphoma of mucosa-associated lymphoid tissue-type (MALT lymphoma) (PCMZL) represent the vast majority of PCBCL and show an indolent slowly progressive course and an excellent prognosis despite a high recurrence rate. Genetic analysis indicates that PCMZL differ from other forms of extranodal MALT lymphomas. The more common class-switched and the non–class-switched form of PCMZL can be distinguished as two distinctive subsets that differ in the cellular composition, IgM expression, and biological behavior with extracutaneous involvement found in the non–class-switched form. Recently, unusual clinical and histological forms of PCMZL and PCFCL manifesting with miliary or agminated lesions have been described that are diagnostically challenging. In contrast to PCMZL and PCFCL, primary cutaneous diffuse large B-cell lymphoma, leg type, and other rare forms of large B-cell lymphomas such as intravascular large B-cell lymphoma have an unfavorable prognosis. There is an emerging group of Epstein–Barr virus (EBV)–driven B-cell lymphoproliferations including posttransplant lymphoproliferative disorders and mucocutaneous ulcer occurring in immunocompromised patients and EBV-associated diffuse large B-cell lymphoma of the elderly arising in the setting of senescence-linked immunodeficiency. This review reports on recent findings expanding the spectrum of clinicopathological features, differential diagnostic aspects, and the pathogenesis of PCBCL and discusses the group of EBV-associated B-cell lymphoproliferations involving the skin.

Key Words: cutaneous lymphoma, B-cell, genetics, diagnosis, WHO, follicle center lymphoma, marginal zone lymphoma, extranodal MALT lymphoma, diffuse large B-cell lymphoma, leg type, intravascular lymphoma, plasmablastic lymphoma, Epstein–Barr virus, immunohistochemistry

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LEARNING OBJECTIVES

After participating in this activity, physicians should be better able to:

1. Identify the characteristics of primary cutaneous B-cell lymphomas (PCBCL).
2. Evaluate the relationship between PCBCL and Epstein-Barr virus.
3. Choose the appropriate differential diagnosis.

CUTANEOUS B-CELL LYMPHOMAS

Primary cutaneous B-cell lymphomas (PCBCL) are the second most common form of primary cutaneous lymphomas (PCL) and account for approximately 25%–30% of all PCL.[1] Both forms of low-grade malignant PCBCL, primary cutaneous follicle center lymphoma (PCFCL) and primary cutaneous marginal zone lymphoma (PCMZL) [extranodal mucosa-associated lymphoid tissue (MALT)-type lymphoma], represent the vast majority of PCBCL and show an indolent slowly progressive course and an excellent prognosis despite a high recurrence rate. In contrast, primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) and other rare forms of large B-cell lymphomas have an impaired prognosis.

The current World Health Organization (WHO) classification (fourth edition, 2008) integrates the achievements of the WHO-European Organization for Research and Treatment of Cancer (EORTC) classification (2005) by pursuing its diagnostic criteria for PCBCL (Table 1). Particularly, PCFCL and PCDLBCL-LT are clearly defined and thus can be reproducibly distinguished by their histology and phenotype.[1–4] By definition, PCBCL are limited to the skin at the time of diagnosis. The indolent forms often remain confined to the skin during their course. In comparison to cutaneous T-cell lymphomas, PCBCL display a more uniform clinical presentation and manifest in most cases with nodules, but plaque-like lesions and papules may be observed. The distribution of the lesions differs between the PCBCL entities, with PCFCL affecting predominantly the head and neck area, whereas PCMZL is typically found on the trunk and arms. The lower extremities, particularly the lower legs, are the predilection site of PCDLBCL-LT. Thus, clinico–pathologic correlation provides important information for the diagnosis. Differentiation of PCMZL and PCFCL from B-cell pseudolymphoma (B-PSL) (synonymously lymphocytoma cutis) is challenging due to a significant overlap of clinical, histological, and phenotypic features. The detection of monotypic plasma cells and/or monoclonal rearrangement of immunoglobulin (Ig)

TABLE 1. Cutaneous B-Cell Lymphomas According to the WHO Classification for Haematopoietic and Lymphoproliferative Disorders (Fourth Edition, 2008) and the WHO-EORTC Classification

WHO-EORTC Classification (2005)	WHO Classification (Fourth Edition, 2008)
Primary cutaneous marginal zone B-cell lymphoma	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Primary cutaneous follicle center lymphoma	Primary cutaneous follicle center lymphoma
Growth patterns: follicular	
Follicular and diffuse	
Diffuse	
	Diffuse large B-cell lymphoma, NOS:
Primary cutaneous diffuse large B-cell lymphoma, leg type	Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lymphoma, other	EBV-positive diffuse large B-cell lymphoma of the elderly
Primary cutaneous intravascular large B-cell lymphoma	Intravascular large B-cell lymphoma
	Plasmablastic lymphoma
	Post-transplant lymphoproliferative disorders (PTLD)

WHO, World Health Organization; WHO-EORTC, World Health Organization-European Organization for Research and Treatment of Cancer.

heavy chain genes (IgH) are considered to be useful adjunctive diagnostic elements for the diagnosis of PCBCL. The BIOMED-2 protocol represents an internationally elaborated and accepted method for the polymerase chain reaction (PCR)–based analysis of Ig heavy chain genes.[5] It has to be emphasized that the molecular data have to be interpreted in the context of clinical, histological, and phenotypic findings. Additional examinations include search for serum antibodies against *Borrelia* species or PCR-based identification of borrelia DNA in cases of PCMZL and Epstein–Barr virus (EBV) by in situ hybridization (EBER), particularly in B-cell infiltrates with centroblastic, immunoblastic, and plasmacytic or plasmablastic differentiation. Staging examinations are essential to exclude secondary cutaneous involvement by nodal or other extranodal B-cell non-Hodgkin lymphomas, with which PCBCL share morphological and immunophenotypic features. Apart from history, hematological and serological tests, staging examinations include radiologic examinations (CT or PET-CT) and bone marrow biopsy. The necessity of bone marrow biopsy in the staging of PCMZL and PCFCL is controversially discussed. The latter should be performed in the workup of high-grade malignant PCBCL such as PCDLBCL-LT or intravascular lymphoma but regarded as optional in low-grade malignant CBCL such as PCFCL and PCMZL according to the International Society for Cutaneous Lymphomas European Organization for Research and Treatment of Cancer (ISCL-EORTC) guidelines.[6] The TNM system proposed by the ISCL-EORTC has been proven to be useful tool to document disease extent in patients with PCBCL and provides prognostic information.[7,8] This review reports on recent findings on clinicopathological features and pathogenetic aspects of PCBCL and the emerging group of EBV-associated B-cell lymphoproliferations.

Primary Cutaneous Marginal Zone Lymphoma

PCMZL is defined as an indolent B-cell lymphoma composed of small B cells, marginal zone cells, lymphoplasmacytoid cells and mature plasma cells.[1,9] In the WHO classification (fourth edition, 2008), PCMZL belongs to the group of extranodal marginal zone lymphoma of MALT lymphoma.[4,10] Recent data, however, indicate that most cases of PCMZL differ from other forms of extranodal MALT lymphoma with regard to the expression of class-switched immunoglobulins, chemokine receptors, translocations, and associated infectious agents.[11,12]

PCMZL manifests in most patients with multifocal nodular lesions, most commonly located on the trunk and arms.[3,13] The nodules are usually less than 3 cm in diameter. Rare clinical variants include an anetodermic form and an agminated form of PCMZL the latter simulating granulomatous rosacea, which both may clinically be misinterpreted as inflammatory diseases.[14–16] The anetodermic form of PCMZL is associated with antiphospholipid antibodies indicating immunologic disorders in a subset of patients.

PCMZL is histologically characterized by confluent nodular lymphocytic infiltrates, which are centered in the dermis and may extend into the subcutis (Fig. 1). The infiltrates are composed of small lymphocytes, lymphoplasmacytoid cells, mature plasma cells, and reactive germinal centers with tingible body macrophages[9,17] (Fig. 2). Marked plasmacytic differentiation and/or a prominent T-cell component may obscure the neoplastic B cells in PCMZL.[18] A subset of PCMZL is characterized by a predominance of monocytoid B cells instead of lymphoplasmacytic cells. Tumor cells express CD20 and bcl-2 but are negative for bcl-6 (Fig. 3).

FIGURE 1. PCMZL (extranodal MALT lymphoma): dermal nodular infiltrates of small lymphocytes, magnification ×10.

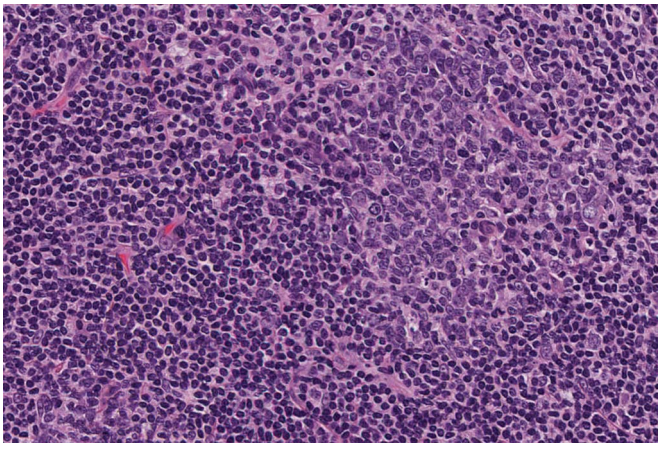

FIGURE 2. PCMZL (extranodal MALT lymphoma): tumor cells with lymphoplasmacytic differentiation and mature plasma cells, magnification ×100.

Two distinctive subsets of PCMZL have recently been delineated[12]: (1) the more common class-switched form of PCMZL with perivascular and periadnexal nodular infiltrates containing plasma cells expressing IgG, IgA, or IgE and numerous T cells in the vast majority of the cases. The reactive follicles express IgD and B cells lack CXCR3. Extracutaneous involvement was not found in the class-switched PCMZL. (2) The rare non–class-switched form of PCMZL histologically presents itself with large nodules of B cells, which express CXCR-3 in half of the cases and show a lower number of admixed T cells. The reactive follicles are IgM positive. Remarkably, in the series reported by Edinger et al, extracutaneous involvement was observed in 3 of 6 cases of the non–class-switched form of MZL.

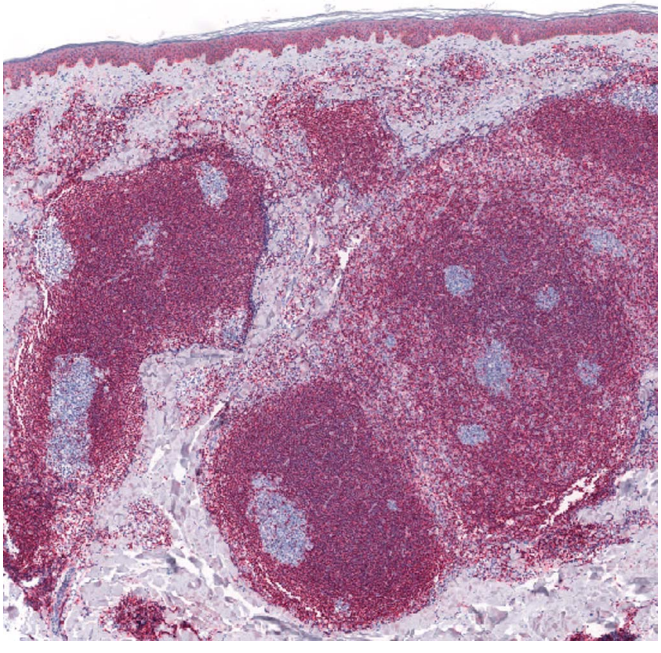

FIGURE 3. PCMZL (extranodal MALT lymphoma): expression of bcl-2 by tumor cells. Reactive germinal centers are spared, magnification ×25.

Due to a significant overlap in clinicopathological features, differentiation of PCMZL from B-PSL is difficult and may be impossible in individual cases. Multifocal presentation, demonstration of monoclonality, and relapsing course are in favor of PCMZL. The observation of multifocal or even miliarial type of B-PSL somehow limits the value of multiple lesions as an argument in favor of PCMZL.[19] Monotypic plasma cells are considered as a major diagnostic criterion for PCMZL, but there is no consensus on the ratio of Ig light chains required for monoclonality. A ratio of 5:1 to 10:1 is considered by most experts as monoclonal. So-called pseudoclonality due to the presence of different B-cell clones, that is, oligoclonal B-cell infiltrates, is a pitfall in the assessment of clonality by PCR and is more commonly found in cases with sparse B-cell infiltrates.[20] Thus, only the demonstration of the same clone in repeated assays proves monoclonality.

Cutaneous involvement by B-cell chronic lymphocytic leukemia (B-CLL) may sometimes simulate PCMZL, but differences in immunophenotype are substantial to distinguish between the 2 disorders. Tumor cells in B-CLL express CD5, CD23, and CD43, whereas PCMZL do not show expression of CD5 and CD43.[21,22] Another potential diagnostic pitfall is secondary cutaneous involvement of other extranodal MALT lymphoma that is histologically and phenotypically similar if not identical with PCMZL. Clinically, PCMZL is more commonly seen in younger patients and favors the trunk and extremities as predilection sites, whereas MZL secondarily involving the skin affects more commonly older patients and involves more often the head/neck regions.[23]

In the WHO-EORTC and the current WHO classifications, the former lymphoma entities, cutaneous immunocytoma and primary cutaneous plasmacytoma, are considered to represent variants of PCMZL.[1,9] Clinically, cutaneous immunocytoma manifests with nodules, which have a smooth surface and may be located on top of acrodermatitis chronica atrophicans. The dense dermal infiltrates are almost exclusively composed of plasma cells with monotypic expression of Ig light chains. Differential diagnosis includes secondary cutaneous infiltrates by extramedullary plasmacytoma. Furthermore, vegetating herpes simplex virus infection in HIV patients may present with ulcerated tumor-like lesions, but they are composed predominantly of mature plasma cells with polytypic Ig light chain expression. The diagnostic epithelial changes pathognomic for alpha-herpesvirus infection may be very subtle and only seen on serial sections.

It remains a matter of debate whether PCMZL represents a de novo neoplastic process or whether B-cell PSL and PCMZL represent different evolutionary steps of a lymphoproliferative reaction to various exogenous and/or endogenous antigens. The association with borrelia infection, the observation of spontaneous involution, and a similar cellular composition of the infiltrate in both B-cell PSL and PCMZL are in favor of the latter concept. The expansion of differing clones in multiple lesions of PCMZL may be due to variable immune response to a chronic antigenic stimulus.[24] Transient proliferations of postgerminal center cells, which are referred to as marginal zone hyperplasia in tonsil and appendix, could

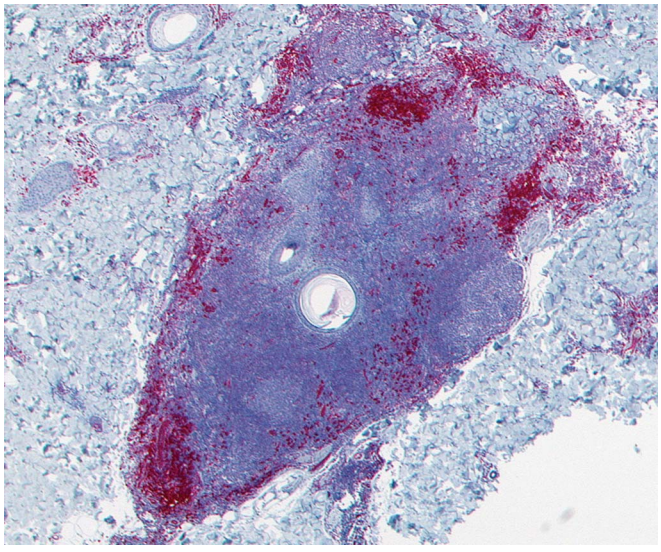

FIGURE 4. PCMZL (extranodal MALT lymphoma): clusters of CD123-positive plasmacytoid dendritic cells in the periphery of the infiltrates. Immunohistochemistry, magnification ×100.

represent an transitional or intermediate step also in the skin, but its relationship to PCMZL remains to be elucidated. At present, the concept of marginal zone hyperplasia in mucosa or skin is limited to lambda light chain restriction and to the observation only in the pediatric population.[25] Detection of plasmacytoid dendritic cells (PDC) arranged in clusters in all cases of PCMZL and in most B-cell PSL suggests common pathogenetic pathways[26] (Fig. 4). We hypothesized that PDC in both processes activate CD4+ T cells and promote survival of antigen-activated T cells which themselves stimulate growth of B cells.[27] The chronically stimulated B cells can undergo somatic hypermutation and additional other genetic alterations, which finally render the process independent of the initial antigenic stimulus as it also has been shown in gastric MALT lymphoma.[10,28] However, in other studies, clusters of PDC were not detected in all cases. For example, Edinger et al[12] identified clusters of PDC only in 1 of the 8 cases studied and in another case, the cells were dispersed, whereas no PDC were noted in the remaining 6 cases.

In a subset of PCMZL cases, *Borrelia* species and hepatitis C virus sequences could be found, but they may be only 2 of several infectious agents linked to PCMZL.[29,30] Nevertheless, even in Europe, PCMZL is only rarely associated with *Borrelia* species[31]

PCMZL has an excellent prognosis with a 5-year survival rate of more than 95%.[3,13] Recurrences are common and occur in up to 50% of the patients but are not linked to an impaired prognosis. Extracutaneous spread is seen in less than 10% of the patient but may be more commonly seen in the non–class-switched subtype of the disease as discussed above.[12] Systemic involvement in PCMZL may be preceded by large cell transformation, which is a rare event in PCMZL.[32] The presence of both the t(14; 18)(q32; q21) IGH/BCL2 and the t(14; 18)(q32; q21) IGH/MALT1 translocations in PCMZL was seen in cases of PCMZL with transformation toward higher-grade B-cell lymphoma.[33]

Primary Cutaneous Follicle Center Lymphoma

Primary cutaneous follicle center lymphoma (PCFCL) represents a tumor of neoplastic follicle center cells and is predominantly composed of centrocyte-like tumor cells with cleaved nuclei.[1] In the current WHO classification (fourth edition, 2008), PCFCL is listed as a separate entity and not only as a variant of extranodal follicular lymphomas.[4] PCFCL affects patients in their fifth to seventh decade with a median age of onset of approximately 50 years and a male to female ratio of 1.5:1. The predilection site is the head and neck area and upper trunk. Erythematous plaques or nodules of firm consistency and a smooth surface represent the most common clinical presentation. In almost 90% of the patients, the disease presents at diagnosis in tumor stage T1 (solitary lesion) or T2 (regional tumoral lesions).[3] PCFCL slowly enlarges and may grow to tumors of large size (up to several centimeters). In some patients, those large tumors may even destroy underlying anatomical structures such as bone.[34] Large tumors of PCFCL on the back have originally been referred to as reticulohistiocytoma dorsi (Crosti's lymphoma). Miliary and agminated type of PCFCL represent a unique and diagnostically misleading clinical presentation of the disease. In a series of 18 patients, all patients presented with multiple, erythematous firm papules arranged in a manner that resembled millet seeds or collected together in small clusters predominantly on the head and neck.[35] Lymphoma was not suspected at initial diagnosis in any of the patients but was confirmed by histology. An anetodermic form has also been observed in PCFCL as a rare variant, in which some of the tumoral lesions regress leaving behind anetoderma.[15]

Histologically, 3 growth patterns can be discerned: a follicular, a follicular and diffuse (mixed), and a diffuse pattern. The follicular pattern is characterized by large neoplastic follicles and is mostly composed of centrocyte-like cells (Figs. 5, 6). In contrast to the reactive germinal centers in B-cell PSL and PCMZL, the neoplastic follicles in PCFCL are devoid of tingible body macrophages in 90% of the cases.[36] The diffuse growth pattern in PCFCL does not represent the consequence of tumor progression from follicular to diffuse pattern. A recent study showed that already the early lesions in diffuse pattern of PCFCL consist mostly of

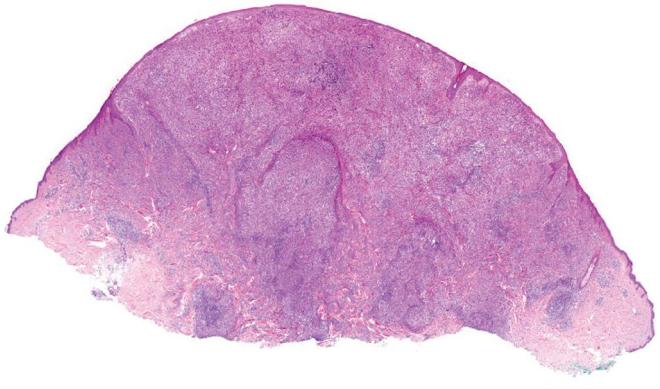

FIGURE 5. Primary cutaneous follicle center lymphoma: nodular infiltrate with large neoplastic follicular structures, magnification ×20.

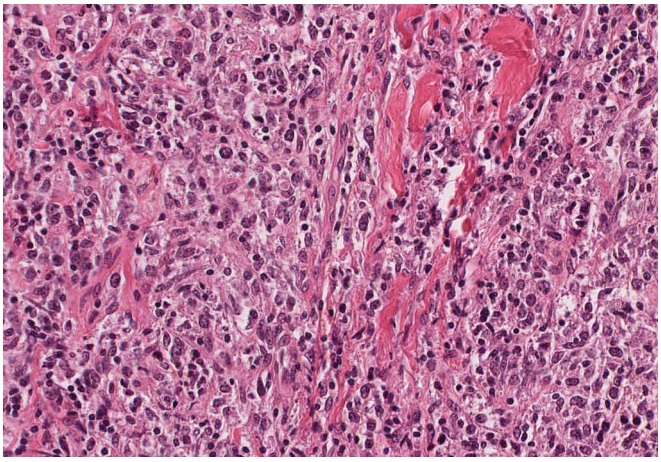

FIGURE 6. Primary cutaneous follicle center lymphoma: centrocyte-like tumor cells with cleaved nuclei, magnification ×250.

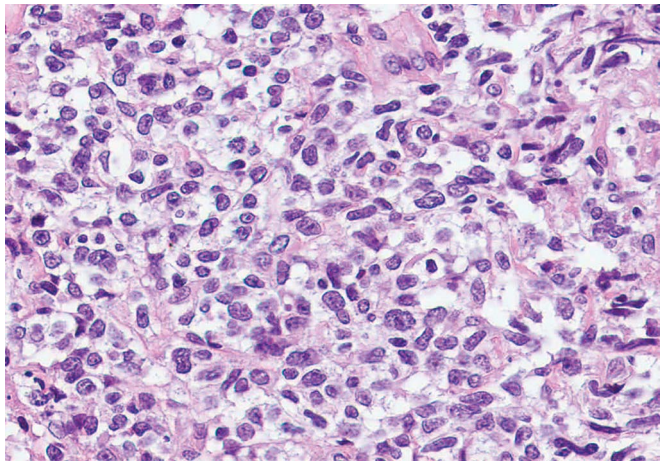

FIGURE 7. Mantle cell lymphoma: secondary cutaneous involvement by tumor cells with centrocyte-like differentiation, magnification ×400.

solitary or clustered papules and small nodules located on the trunk and presented with the characteristic histological features, that is, aggregates of medium and large centrocytes admixed with small lymphocytes without the formation of follicular structures.[37] The tumor cells in PCFCL express B-cell markers (CD20, Pax5) and bcl-6 in all cases. Expression of bcl-2, which is a characteristic feature of nodal follicular lymphoma, is found in only a minority (approximately 10%–20%) of PCFCL.[38] In PCFCL, the presence or absence of bcl-2 expression and/or t(14; 18) translocation is not linked to differences in clinical presentation or prognosis.[1] The expression of bcl-2 should always raise the suspicion for secondary cutaneous infiltrates of a nodal follicular lymphoma. Proliferating cells (Ki-67+ or MIB-1+) are scattered throughout the entire infiltrate, which contrasts the high proliferative activity centered in the reactive germinal centers in B-PSL. Large irregular networks of CD21-positive follicular dendritic cells (FDC) are seen in the follicular form. Remnants of these networks are also discernible in PCFCL with diffuse growth pattern, whereas primary cutaneous diffuse large B-cell lymphoma, leg type (PCDLBCL-LT) lacks networks of FDC. Monoclonal rearrangement of IgH genes can be detected in up to 90% of the cases using BIOMED-2 primers.[39] Secondary cutaneous involvement by mantle cell lymphoma, which accounts for approximately 10% of nodal B-cell Non-Hodgkin lymphoma, has to be considered in the differential diagnosis. It presents with disseminated macules, papules, plaques, or nodules.[40] The diffuse infiltrates are composed of blasts or centrocyte-like tumor cells and therefore may mimic PCFCL[41] (Fig. 7). Phenotypic analysis is very useful, because the tumor cells in mantle cell lymphoma express CD5 and cyclin D1, which are both negative in PCFCL and PCMZL. In addition, the tumor cells in mantle cell lymphoma are negative for CD23 in contrast to B-CLL.

Importantly, some B-PSL located at certain anatomic sites such as the nipple and scrotum often show features accounting for a significant overlap with PCFCL.[42,43] In those cases, coalescing lymphoid follicles with nonpolarized germinal centers lacking mantle zones and smudged infiltrates of lymphoid cells spreading into collagen (often as single-cell files), smooth muscle, vessel walls, and peripheral nerve sheaths may result in diagnostic challenge and mimic PCFCL.

Although recurrences are seen in up to 40% of the patients with PCFCL, this form of PCBCL has an excellent prognosis with a 5-year survival rate of more than 90%.[1,3] Extracutaneous spread occurs rarely, that is, in approximately 10% of the patients. PCFCL arising at the legs and those cases with expression of FOX-P1 seem to have a worse prognosis and should be treated more aggressively similar to DLBCL-LT.[6] CBCL with spindle cell morphology, some of them belonging to PCFCL, others to PCDLBCL, may require higher attention for extracutaneous spread.[44]

Primary Cutaneous Diffuse Large B-Cell Lymphoma

Primary cutaneous diffuse large B-cell lymphoma (DLBCL) is characterized by dense nodular or diffuse infiltrates predominated by centroblast-like and immunoblast-like tumor cells with noncleaved, that is, round nuclei.

The *DLBCL-LT* represents the most common type of DLBCL and is listed as a distinct subtype of DLBCL in the current WHO classification (fourth edition, 2008). In 80% of the patients, DLBCL-LT manifests with solitary or multiple rapidly growing nodules located on the legs, particularly on the lower legs (Fig. 8). DLBCL-LT affects elderly patients in their seventh and eight decades with a strong female preponderance (male to female ratio, 1: 3–4). Histologically, DLBCL-LT shows diffuse infiltrates of centroblast- and immunoblast-like cells with mitotic activity (Figs. 9, 10). There are only few admixed small lymphocytes or other reactive cells. Uncommon histological presentations include epidermotropic, angiocentric, anaplastic, and spindle cell variants.[45] Phenotypically, tumor cells in DLBCL-LT strongly express bcl-2 and MUM-1, but in most cases, they show weak expression of bcl-6 or are negative for bcl-6 and CD10[46] (Fig. 11).

FIGURE 8. PCDLBCL-LT: solitary large tumor on the lower leg.

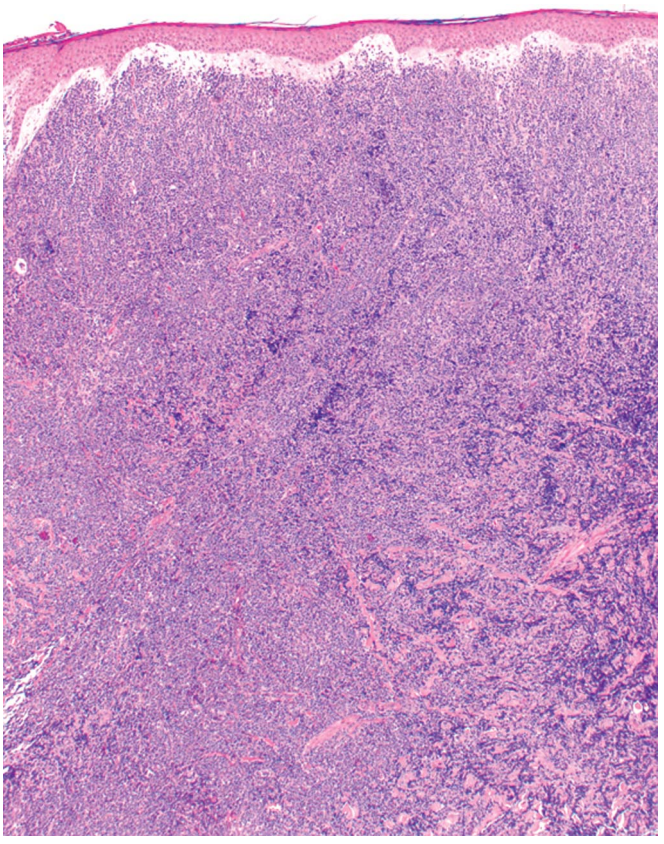

FIGURE 9. PCDLBCL-LT: dense diffuse infiltrates in the entire dermis, magnification ×20.

IgM expression was identified as an additional adjunctive diagnostic marker, which is found in all cases of DLBCL-LT but only rarely in PCFCL (9%).[47] In contrast to PCFCL, networks of CD21-positive FDC are not found in DLBCL-LT. In regard to the prognostic and therapeutic implications, the most relevant differential diagnosis of DLBCL-LT is PCFCL with diffuse growth pattern that is based on cytomorphology (centrocyte-like vs. centroblast- and immunoblast-like differentiation) and the phenotype (bcl-2, bcl-6, MUM-1, IgM) (for review see also ref. 48) (Table 2). MUM-1 is diffusely positive in DLBCL-LT that is helpful while differentiating the disease from PCFCL in which neoplastic cells are negative or display a low expression of MUM-1. FoxP1 is also a useful marker to this end. A diagnostic pitfall may result from CD30 expression in large B-cell lymphoma mimicking anaplastic large T-cell lymphoma, but expression of CD20 and absence of T-cell markers lead to the diagnosis.[49,50]

In contrast to low-malignant CBCL such as PFCFL and PCMZL, DLBCL-LT has a poor prognosis with 5-year survival rates ranging from 20% to 60%.[51] Genetic analysis revealed chromosomal loss of 9p21, which encodes p16, as a negative prognostic marker in PCDLCBL-LT.[52] Loss of p16 assessed by immunohistochemistry, however, does not correlate with these findings indicating the necessity for genetic analysis by reverse transcription–PCR or fluorescence in situ hybridization analysis. Recurrent deletions in 9p21 (p14 (ARF)/p16(INK4a/CDKN2A) have been found to be a constant finding in DLBCL-LT, whereas PCFCL does not exhibit this change.[53] Factors indicating a poor prognosis in DLBCL-LT include the presence of multiple tumors, involvement of both legs, chromosomal loss of 9p21, and activation of nuclear factor κB pathway with inhibition of antiapoptotic proteins.[51,52,54] DLBCL-LT requires chemotherapy in combination with rituximab, particularly in patients with multiple

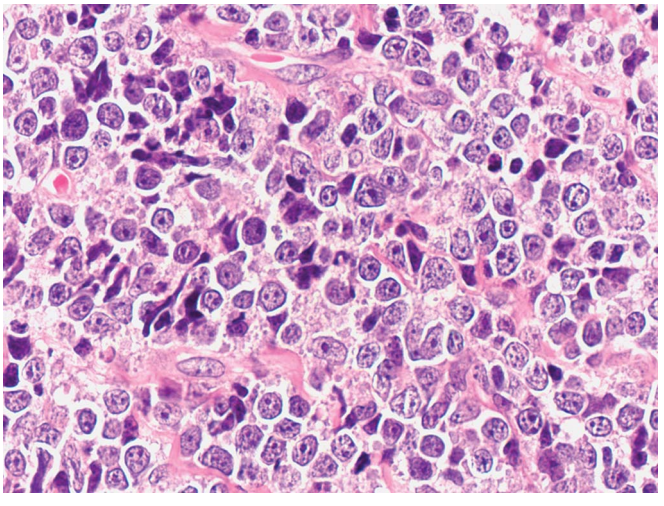

FIGURE 10. PCDLBCL-LT: the tumor cells display a centroblast-like and immunoblast-like differentiation, magnification ×400.

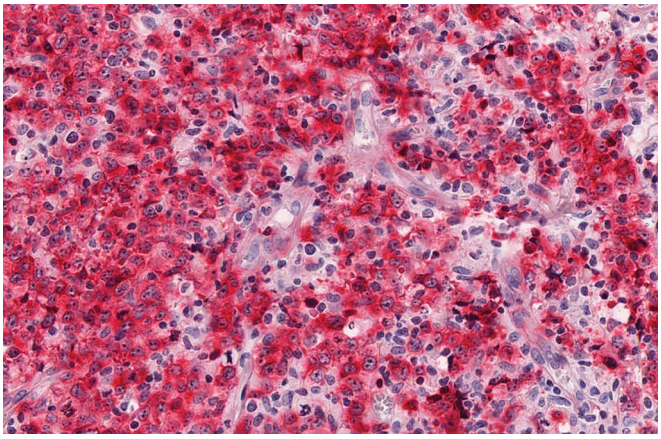

FIGURE 11. PCDLBCL-LT: the tumor cells show strong expression of bcl-2, magnification ×250.

tumors.[6] Solitary lesions may be excised and/or treated by radiation.

The term *primary cutaneous DLBCL, other* refers to cases of large B-cell lymphomas not belonging to DLBCL-LT.[1] Primary cutaneous DLBCL, other, is a very rare and still poorly characterized form of DLBCL that shares cytological features with DLBCL-LT, that is, infiltrates composed of centroblast- and immunoblast-like cells but differ in regard to the phenotype[1] with expression of bcl-6 in all cases, MUM-1 in 67%, and FOX-P1 in 50% of the cases. In sharp contrast to DLBCL-LT tumor cells in DLBCL, others are negative for bcl-2 (Table 3). Occasionally, numerous small lymphocytes in addition to the large centroblast- and immunoblast-like tumor cells may be present in DLBCL, other (Fig. 12). Furthermore, DLBCL, other includes morphological variants such as anaplastic or plasmablastic subtypes of DLBCL or T-cell/histiocyte-rich large B-cell lymphomas.[1]

Intravascular large B-cell lymphoma is a rare form of extranodal large B-cell lymphoma. As the designation implies, intravascular large B-cell lymphoma is characterized by the intravascular growth of large B cells especially in small vessels, particularly capillaries and venules.[55] A defect in homing receptors on tumor cells (CD29 = beta1 Integrin; CD54 = ICAM1) is considered to be responsible for the unique intravascular growth pattern.[56] Any organ can be involved, although lymph nodes are usually spared. Skin involvement manifests with livedo-like reticular erythema, panniculitis, or painful telangiectasias simulating inflammatory diseases or with nodules.[57] Clinical symptoms include B symptoms (fever, night sweat, weight loss) in half of the patients and neurologic deficits. A systemic and a cutaneous form are distinguished. The cutaneous form displays a better prognosis with 3-year survival rate of 56% compared with systemic form (33%).[55] In the skin, small dermal and subcutaneous vessels are filled with large B cells with pleomorphic, moderately chromatin dense nuclei and abundant cytoplasm (Fig. 13). Occasionally, tumor cells colonize hemangiomas.[58,59]The tumor cells express CD20 and bcl-2 and may be positive for CD5 and/or CD10. A rare T-cell and natural killer (NK) cell variant of intravascular lymphomas has been described and is associated in some cases with EBV.[60] Iacobelli et al[61] reported on a case of intravascular anaplastic large cell lymphoma restricted to the skin. The T-cell and NK-cell variant is not included as a distinct entity or subtype in the current WHO classification. Differential diagnosis includes intralymphatic histiocytosis as it can be seen after orthopedic metal implantation.[62] Benign intravascular CD30+ T-cell proliferation occurring after trauma or as a consequence of inflammatory skin diseases has to be differentiated from the rare T-cell variant of intravascular lymphoma.[63,64]

EBV-Associated B-Cell Lymphoproliferations

EBV is a γ-herpesvirus that is pathogenetically linked to the development of several B-cell, T-cell, and NK-cell lymphoproliferative disorders. Among the increasing spectrum of EBV-associated B-cell lymphoproliferations, EBV-positive DLBCL of the elderly, plasmablastic lymphoma (PBL), EBV-positive mucocutaneous ulcer, and lymphomatoid granulomatosis (LYG) are of particular dermatopathologic interest.

EBV-positive DLBCL of the elderly is an EBV-positive B-cell lymphoma that occurs in patients older than 50 years of age (with a median age of 71 years) and without any known immunodeficiency or previous lymphoma. Nevertheless, the immunological deterioration or senescence in immunity as part

TABLE 2. Primary Cutaneous Follicle Center Lymphoma and—Histological and Phenotypic Features

	Primary Cutaneous Follicle Center Lymphoma	Primary Cutaneous Diffuse Large B-Cell Lymphoma, leg type
Clinical features	Nodules and surroundings plaques mostly on the head and neck or upper trunk	Ulcerated large nodules mostly on the lower legs
Histology	Predominantly centrocyte-like cells	Predominantly centroblast- and immunoblast-like cells
Phenotype	CD20/CD79a/Pax5	CD20/CD79a/Pax5
	bcl-6+	bcl-6−/+
	bcl-2−	bcl-2++
	MUM-1-	MUM-1+
	IgM−	IgM+
	CD21/CD35: irregular networks or remnants of FDC networks	CD21/CD35: lack of FDC networks
Prognosis	Favorable: 5-year survival rate: 95%	Poor: 5-year survival rate: 20%–60%

FDC, Follicular dendritic cells.

TABLE 3. Immunophenotypic Features in Primary Cutaneous Follicle Center Lymphoma, Diffuse Growth Pattern (PCFCL) in Comparison to PCDLBCL-LT and DLBCL, other. The Percentages of Markers Are Based on the Data Published in the Literature.[46,47,90,91]

Cytomorphology	Centrocyte-Like Cells		Centroblast- and Immunoblast-Like Cells		
	FCL, Diffuse		PCDLBCL, Leg Type		DLBL, Others
Site	Nonleg, 90%	Leg, 10%	Leg, 80%	Nonleg, 20%	Leg/Nonleg, 56%/44%
Marker (%)					
Bcl-2	7–22	40	93–100	67–70	0
Bcl-6	93	67	57–75	80	100
MUM-1	0–7	57	76–92	41–75	67
FOXP1	10	20	72–80	100	50
CD10	7–18	0	0	0	14

of the aging process is assumed to play a pathogenetic role in the development of this lymphoma, which involves most commonly extranodal sites (70%), especially skin, lung, tonsil, and stomach.[65]

Histologically, diffuse infiltrates of immunoblast-like and/or plasmablast-like cells with intermingled tingible body macrophages and geographic necroses are seen. The tumor cells express B-cell markers (CD20, CD79a, Pax-5) and MUM-1/IRF4 but generally lack expression of CD10 and bcl-6. CD30 expression and Ig light chain restriction are variable. The tumor cells show a high proliferation rate. Association with EBV is best demonstrated by the detection of EBER using in situ hybridization, but some of the cases also show expression of latent membrane protein 1 and EBNA-2.[66,67] The disease runs an aggressive course with a median survival of 2 years.[66] EBV-positive DLBCL of the elderly and PBL share overlapping features.[68,69]

Plasmablastic lymphoma (PBL) is a rare variant of DLBCL that almost exclusively develops in the setting of HIV infection or other immune deficiencies including post-transplant. An etiological role for EBV has been established. PBL mostly manifests in the oral cavity but also involves the skin on rare occasion. To date, less than 30 PBL cases presenting in the skin have been documented.[69–71] Risk factors for the development of the lymphoma in the setting of organ transplantation include younger age, higher rejection frequency, and high-dose cyclosporine therapy. Occurrence in apparently immunocompetent previously healthy patients is exceptional. The disease is characterized by an aggressive course with mean survival of 6 months. HIV-infected patients seem to have a more favorable prognosis compared with patients after transplantation. In addition, more recently, human herpesvirus 8 (HHV-8) has also been implicated in this lymphoma type.[72]- Clinically, cutaneous involvement is characterized by solitary or multiple asymptomatic skin-colored or violaceous nodules and papules located on the trunk and limbs ranging in size from 0.5 to 12 cm. Large ulcerated tumors on the lower legs clinically simulating DLBCL-LT have been described.[69] Histologically, there is a diffuse or multinodular proliferation composed of immunoblast-like cells or markedly atypical cells with plasmacytic differentiation, that is, eccentrical nucleus with a "clock-faced" chromatin, a discrete perinuclear hof and abundant cytoplasm (Fig. 14). Multinucleated forms (binucleated and trinucleated forms) can be observed. Some of the tumor cells manifest a frankly blastic appearance with more centrally located nuclei and finely dispersed chromatin. Mitotic figures are usually numerous and atypical. Immunohistochemically, the neoplastic cells express plasma cell markers including CD38, CD138, and VS38c, whereas they lack expression of B-cell markers such as CD20 and Pax-5. Variable expression is seen with CD10, CD79a, CD30, and CD56. EBV has been

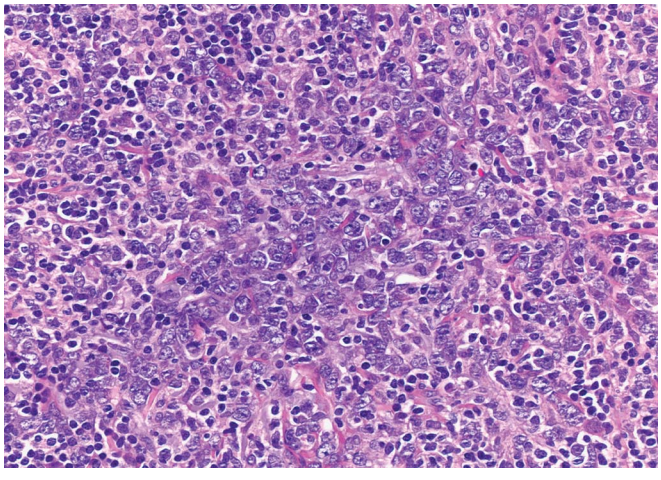

FIGURE 12. Primary cutaneous diffuse large B-cell lymphoma, other: tumor cells with centroblast-like differentiation intermingled with numerous small lymphocytes, magnification ×200.

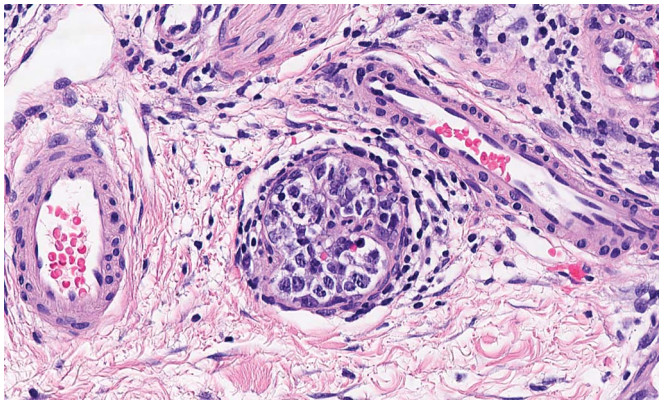

FIGURE 13. Intravascular large B-cell lymphoma: large atypical B cells in the lumen of a small dermal vessel, magnification ×250.

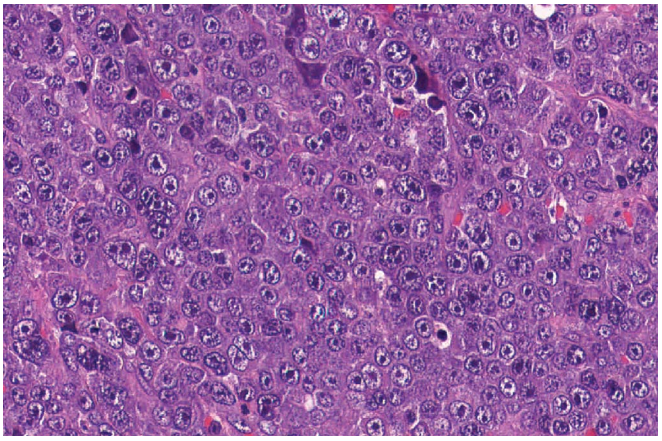

FIGURE 14. PBL: diffuse monomorphic infiltrate of large immunoblastic tumor cells with prominent central nucleolus, magnification ×400.

demonstrated in a majority of cases with EBER transcripts often found in virtually all tumor cells (Fig. 15).

Posttransplant lymphoproliferative disorder represents a spectrum of lymphoid diseases, ranging from early lesions, such as plasmacytic hyperplasia, to monomorphic neoplasms. Fifty cases of primary cutaneous B-cell posttransplant lymphoproliferative disorder were recently reviewed.[73] They usually manifest several years after transplantation, show a male preponderance, tend to occur on extremities, are frequently EBV associated, and were associated with a favorable clinical outcome. Histologically, some of these cases show plasmacytoma-like features.[74,75] Similar B-cell lymphoproliferations in patients with drug-related immunosuppression outside of organ transplantation have been reported.[50,76,77] They mostly have a large cell morphology and may be associated with EBV.

Lymphomatoid Granulomatosis

LYG is a rare B-cell proliferation with primarily extranodal involvement, affecting the lungs, skin, CNS, and the kidneys.[78] The skin is secondarily involved in 20%–50% of LYG patients. The cutaneous manifestations may include papulonodular lesions, subcutaneous infiltrations, ulcerations, and facial edema.[79,80] Histologically, angiocentric infiltrates with large atypical B cells are found in a background of a dense infiltrate of reactive T cells, histiocytes, and plasma cells.[81,82] Association with EBV is found in most of the cases with EBER transcripts present in B cells.

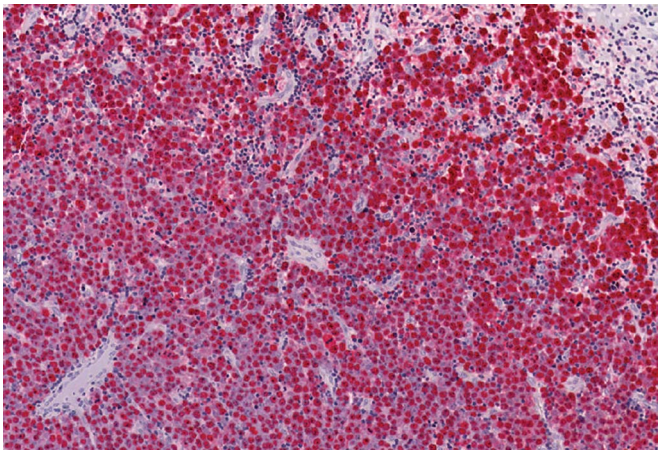

FIGURE 15. Plasmablastic lymphoma: EBER transcripts in the nuclei of virtually all tumor cells. In situ hybridization, magnification ×200.

EBV-positive mucocutaneous ulcer is a recently described B-cell lymphoproliferative disease that manifests with isolated sharply demarcated ulceration most commonly in the oropharynx, skin, and gastrointestinal tract.[83] A third of the affected patients has a drug-related immunosuppression, but age-related immune suppression is also a feature.[83,84] Polymorphous infiltrates of atypical large B-cell blasts, often with Hodgkin or Reed-Sternberg cell-like morphology in the background of abundant small T cells and eosinophils, are found. The large cells express CD20 and CD30 and are positive for EBER. Spontaneous regression was observed in half of the patients and occurred on withdrawal of immunosuppressive drugs. Relapses were rare, and complete remission was seen in all patients. A case of EBV-positive + mucocutaneous ulcer with concomitant TCR-γ/IgH rearrangements has recently been reported[85] thereby extending the spectrum of lymphoproliferations with dual genotype.[86] EBV-positive mucocutaneous ulcer has to be distinguished from traumatic ulcerative granuloma with stromal eosinophilia, which harbors CD30+ T cells in more than half of the cases (71%) and clonal T cells in 24% of the cases, and may represent a CD30+ T-cell lymphoproliferations in the oral mucosa.[87–89]

In summary, PCBCL represent a morphologically and prognostically heterogenous group of B-cell proliferations. Clinicopathological correlation, phenotyping, and staging examinations are essential diagnostic elements in the diagnostic workup of PCBCL. Genetic profiling allows to identify subsets with a more aggressive behavior. EBV may be involved particularly in B-cell proliferations arising in immunosuppressed patients.

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CME EXAMINATION
MARCH 2014

Please mark your answers on the ANSWER SHEET.

After completing this CME activity, physicians should be better able to diagnose the cutaneous deposition disorders, distinguish the clinical, histopathologic and immunohistochemical features of these often-confusing entities, classify lesions into one of the five categories of cutaneous deposits, and identify the specific substance involved in the cutaneous deposit.

1. Which statement about primary cutaneous marginal zone lymphoma (PCMZL) is correct?

a) Cutaneous infiltrate of B-cell chronic lymphocytic leukemia is an important histologic differentialdiagnosis.
b) PCMZL is commonly associated with borrelia infection.
c) PCMZL more commonly affects older patients (>70 years).
d) The lack of monoclonal plasma cells excludes the diagnosis of PCMZL.

2. Which statement about primary cutaneous follicle center cell lymphoma (PCFCL) is correct?

a) The tumor cells in PCFCL express bcl-2 in the majority of the cases.
b) PCFCL arising at the legs have a worse prognosis.
c) The 5-year survival rate of PCFCL is about 60%.
d) Immunohistochemistry is not helpful in differentiating PCFCL from cutaneous infiltrates of mantle cell lymphoma.

3. Diffuse large B-cell lymphoma, leg-type (DLBCL-LT):

a) Is typically positive for bcl-2 and MUM-1.
b) Lacks expression of cyclin D1.
c) With chromosomal loss of 9q21 (encodes p16) shows a worse prognosis
d) Mostly affects younger patients (<40 years)

4. Which of the following is not a differential diagnosis of intravascular large B-cell lymphoma?

a) Lymphangiosis carcinomatosa
b) Intralymphatic histiocytosis
c) Cryoglobulinemia
d) Intravascular CD30-positive T-cell proliferation

5. Which statement regarding EBV-associated B-cell lymphoproliferations is correct?

a) In the setting of organ transplantation, advanced age is a risk factor for the development of plasmablastic lymphoma (PBL).
b) In EBV-positive mucocutaneous ulcer the neoplastic cells express CD20 and CD30, but are negative for EBER.
c) PBL is almost exclusively found in patients with HIV infection or other immune deficiencies.
d) The prognosis of PBL is favourable.

ANSWER SHEET FOR THE AMERICAN JOURNAL OF DERMATOPHATHOLOGY
CME PROGRAM EXAM
March 2014

Please answer the questions on page 208 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____
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1. (A) (B) (C) (D) (E)
2. (A) (B) (C) (D) (E)
3. (A) (B) (C) (D) (E)
4. (A) (B) (C) (D) (E)
5. (A) (B) (C) (D) (E)

Your evaluation of this CME activity will help guide future planning. Please respond to the following questions below.

Please rate these activities (1 — minimally, 5 — completely)	1 2 3 4 5
These activities were effective in meeting the educational objectives	O O O O O
These activities were appropriately evidence-based	O O O O O
These activities were relevant to my practice	O O O O O

Please rate your ability to achieve the following objectives, both before and after this activity: 1 (minimally) to 5 (completely)

	Pre 1 2 3 4 5	Post 1 2 3 4 5
1. Identify the characteristics of primary cutaneous B-cell lymphomas (PCBCL).	O O O O O	O O O O O
2. Evaluate the relationship between PCBCL and Epstein-Barr virus.	O O O O O	O O O O O
3. Choose the appropriate differential diagnosis.	O O O O O	O O O O O

How many of your patients are likely to be impacted by what you learned from this activity?
O <20% O 20-40% O 40-60% O 60-80% O >80%

	1 2 3 4 5	1 2 3 4 5
Do you expect that these activities will help you improve your skill or judgment within the next 6 months? (1 — definitely will not change, 5 — definitely will change)	O O O O O	O O O O O

How will you apply what you learned from these activities (mark all that apply):

In diagnosing patients O	In making treatment decisions O
In monitoring patients O	As a foundation to learn more O
In educating students and colleagues O	In educating patients and their caregivers O
As part of a quality or performance improvement project O	To confirm current practice O
For maintenance of board certification O	For maintenance of licensure O

	1 2 3 4 5
How committed are you to applying these activities to your practice in the ways you indicated above? (1 — minimally, 5 — completely)	O O O O O

	Yes	No
Did you perceive any bias for or against any commercial products or devices? If yes, please explain:	O	O

How long did it take you to complete these activities? _____ hours _____ minutes
What are your biggest clinical challenges related to dermatopathology?

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